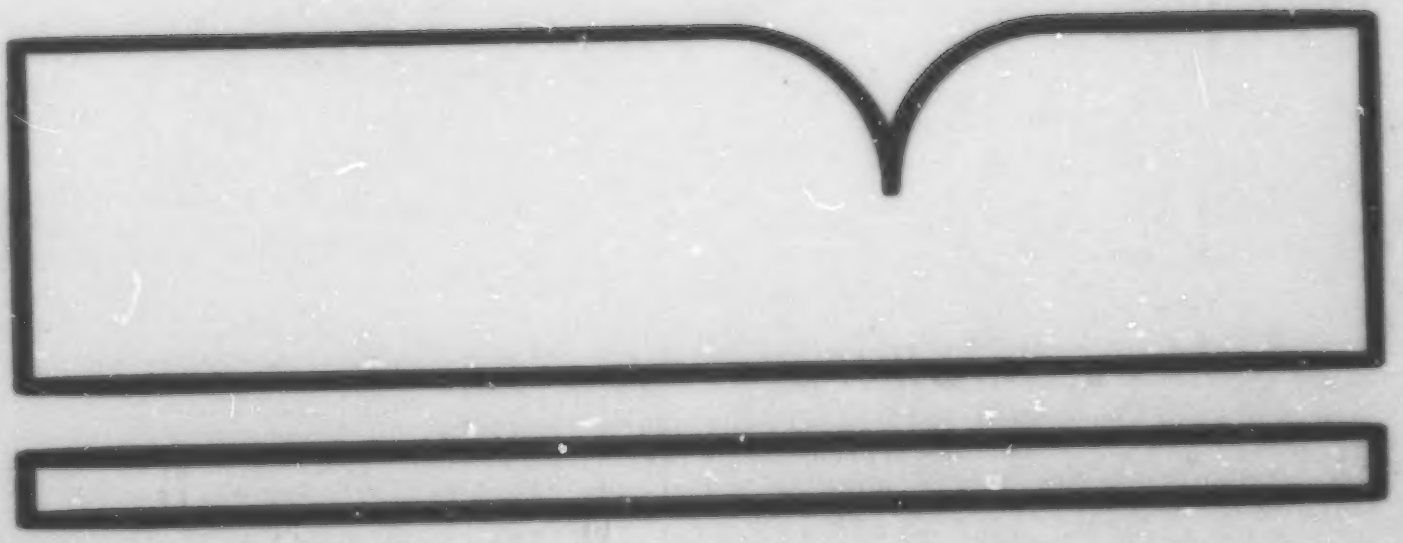
PB88-179924

Health Effects Assessment for Methyl Isobutyl Ketone

(U.S.) Environmental Protection Agency
Cincinnati, OH

Apr 87



U.S. Department of Commerce
National Technical Information Service

PB88-179924

EPA/600/8-88/045
April, 1987

HEALTH EFFECTS ASSESSMENT FOR METHYL ISOBUTYL KETONE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/600/8-88/045		PB88 179924/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
Health Effects Assessment for Methyl Isobutyl Ketone	April 1987
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Public	Unclassified	34
	20. SECURITY CLASS (This page)	22. PRICE
	Unclassified	PC $12.95 / A6.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with methyl isobutyl ketone. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Hazard Profile for Methyl Isobutyl Ketone. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986a. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Methyl Isobutyl Ketone. Online (verification date 5/30/86, data input pending). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Chronic toxicity and carcinogenicity data for MIBK by both oral and inhalation exposures are lacking. A 13-week rat gavage study (Microbiological Associates, 1986) provides the only available subchronic oral toxicity data for MIBK and defines a NOAEL of 50 mg/kg/day. Higher doses caused increased relative kidney and liver weights and general nephropathy. Using this NOAEL, RfD_{SO} and RfD_{O} values of 0.5 and 0.05 mg/kg/day (35 and 3.5 mg/day for a 70 kg human), respectively, were calculated.

An RfD_{SI} of 14 mg/day and an RfD_{I} of 1.4 mg/day were calculated from a NOAEL in rats exposed 6 hours/day, 5 days/week at 50 ppm (205 mg/m^3) for 14 weeks (Union Carbide Corp., 1983b). At a higher exposure level, 250 ppm (1024 mg/m^3), hyaline droplets in the proximal tubules of the kidneys were observed. A CS of 11.5 was calculated for the occurrence of hyaline droplets in kidneys of rats exposed at this higher level.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

TABLE OF CONTENTS

		Page
1.	ENVIRONMENTAL CHEMISTRY AND FATE	1
2.	ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS	3
2.1.	ORAL	3
2.2.	INHALATION	3
3.	TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS	4
3.1.	SUBCHRONIC	4
3.1.1.	Oral	4
3.1.2.	Inhalation	5
3.2.	CHRONIC	7
3.2.1.	Oral	7
3.2.2.	Inhalation	7
3.3.	TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS	8
3.3.1.	Oral	8
3.3.2.	Inhalation	8
3.4.	TOXICANT INTERACTIONS	9
4.	CARCINOGENICITY	11
4.1.	HUMAN DATA	11
4.2.	BIOASSAYS	11
4.3.	OTHER RELEVANT DATA	11
4.4.	WEIGHT OF EVIDENCE	11
5.	REGULATORY STANDARDS AND CRITERIA	12
6.	RISK ASSESSMENT	13
6.1.	SUBCHRONIC REFERENCE DOSE (RfD_S)	13
6.1.1.	Oral (RfD_{SO})	13
6.1.2.	Inhalation (RfD_{SI})	13
6.2.	REFERENCE DOSE (RfD)	14
6.2.1.	Oral (RfD_O)	14
6.2.2.	Inhalation (RfD_I)	14
6.3.	CARCINOGENIC POTENCY (q_1^*)	17
7.	REFERENCES	18
APPENDIX:	Summary Table for MIBK	24

LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effect dose
MIBK	Methyl isobutyl ketone
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposed level
TLC	Taurolithocholate
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of MIBK are presented in Table 1-1.

The atmospheric half-life of MIBK is based on its reaction with photochemically generated HO radical. The atmospheric half-life was calculated using measured hydroxyl reaction rate constants of $(1.24\text{-}1.52)\times10^{-11}$ cm^3/molecule-sec and an ambient HO radical concentration of 8×10^5 molecules/cm^3. Biodegradation, photolysis and volatilization are possible mechanisms by which MIBK may be removed from aqueous systems (Lande et al., 1976); however, the overall rate of removal could not be located in the available literature. The volatilization half-life from agitated water 1 m deep was calculated to be 16.8 hours using the measured mass transfer coefficient for MIBK and O_2 at 25°C (Rathbun and Tai, 1982). Based on its relatively high water solubility and low soil adsorption coefficient, MIBK is predicted to be highly mobile in soil (Swann et al., 1984). Monitoring data reveal that this compound has been identified in leachates from landfills and could potentially contaminate groundwater (Francis et al., 1980; Sawhney and Kozloski, 1984).

TABLE 1-1

Selected Physical and Chemical Properties and Half-Lives for MIBK

Property	Value	Reference
CAS number:	108-10-1	
Chemical class:	saturated aliphatic ketone	
Molecular weight:	100.16	
Vapor pressure:	15 mm Hg at 20°C	Lande et al., 1976
Water solubility:	2.04×10^4 ℓ at 20°C	Lande et al., 1976
Log octanol/water partition coefficient:	1.09 (estimated)	Hansch et al., 1968
or		
Bioconcentration factor:	2 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	19 (estimated)	Lyman et al., 1982
Half-life in air:	<1 day	Cox et al., 1980; Darnall et al., 1976

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Acute toxicity studies in animals indicate that MIBK is absorbed from the gastrointestinal tract (U.S. EPA, 1980a). DiVincenzo and Krasavage (1974) have shown that MIBK is metabolized in guinea pigs and is excreted in the urine.

2.2. INHALATION

Acute toxicity studies in animals indicate that MIBK is absorbed from the respiratory tract (U.S. EPA, 1980a). MacEwen et al. (1971) exposed rats, dogs, monkeys and mice by inhalation to 100 or 200 ppm MIBK for 2-week periods. The results of these studies indicated that MIBK is absorbed from the respiratory tract and excreted primarily through the kidney.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Microbiological Associates (1986) conducted a 13-week study in which groups of 30 male and 30 female Sprague-Dawley rats received gavage doses of 0, 50, 250 or 1000 mg/kg/day MIBK in corn oil. Extensive analyses of hematological parameters, clinical chemistry and urine chemistry were performed on 10 rats/sex from each treatment, along with histopathological examination of all major tissues. The only clinical sign of toxcity was lethargy which occurred only in high-dose rats of both sexes. Two high-dose females and one control female died during the study. There was a slight (9%) reduction in body weight gain among high-dose males. Slight hemoconcentration occurred in females given 250 or 1000 mg/kg/day. Hypoglycemia and hypercholesterolemia occurred in females given 250 mg/kg/day and to a greater extent in both sexes at 1000 mg/kg/day. No other hematological or clinical chemistry parameters were affected. Generalized nephropathy and increased relative kidney weights occurred in both sexes at 1000 mg/kg/day. Relative kidney weights were also increased, but to a lesser extent, in the 250 mg/kg/day groups. Hepatomegaly occurred in both sexes at 1000 mg/kg/day and possibly in males at 250 mg/kg/day. No treatment-related histopathological lesions were found in the liver or any other tissue. The authors concluded that 50 mg/kg/day for 13 weeks was a NOEL for rats in this study.

In a study by Union Carbide Corporation (1983a), groups of five female Wistar rats were exposed to drinking water containing 0 or 1.3% MIBK (1.04 g/kg/day) for 120 days. Rats were examined for neurological effects and body weights were recorded at regular intervals throughout the study.

Necropsies were performed after terminal sacrifice and animals were examined for neuropathy and muscle atrophy. The only effect noted in MIBK-treated rats was a significant ($p<0.05$) increase in kidney weights as compared with controls.

3.1.2. Inhalation. Silverman et al. (1946) exposed 12 male and female volunteers to MIBK vapors for 15-minute periods. According to most of the volunteers, 100 ppm (410 mg/m³) was the highest tolerable concentration for 8 hours. At 200 ppm (820 mg/m³), the odor was objectionable and the vapor was irritating to the eyes.

MacEwen et al. (1971) conducted inhalation experiments with rats, dogs, mice and monkeys exposed to MIBK. Initial 2-week range-finding studies were performed with groups of 4 monkeys, 8 dogs, 40 mice and 50 rats exposed continously to 100 or 200 ppm (410 or 820 mg/m³) MIBK. Controls consisted of 3 monkeys, 4 dogs, 20 mice and 25 rats. No obvious toxic effects were observed and no gross pathology, hematological effects or clinical chemistry effects occurred. The only observed effects were increased relative kidney weights of rats at both doses, and increased relative liver weights of high-dose rats.

In a subsequent study, MacEwen et al. (1971) exposed groups of 100 male Wistar rats, 8 male beagle dogs, 2 male monkeys (Macaca mulata) to 0 or 410 mg/m³ MIBK vapors continously for 90 days. Because the purpose of the study was to investigate possible effects of MIBK vapors released from plastics in a space cabin environment, the experiment was conducted under simulated atmospheric conditions (i.e., oxygen-rich environment, low atmospheric pressure). The gas mixture was 68% oxygen and 32% nitrogen and the pressure was 5 psia. Dogs and monkeys were unaffected by MIBK exposure,

evidenced by hematological and clinical chemistry measurements and histopathological examinations. The growth rate of rats appeared to be unaffected by treatment. Control and treated rats appeared to average 0.35 kg during the experiment (estimated from graphic presentation of growth curve). Rats exposed to MIBK had increased relative liver and kidney weights. All exposed rats had hyaline droplet degeneration of the proximal tubules with occasional tubular necrosis. These results suggest that rats are more sensitive to MIBK than dogs and monkeys; however, these results are of questionable relevance to environmental exposures and risk assessment because of the specialized conditions under which this experiment was conducted.

Union Carbide Corporation (1983b) exposed groups of 14 males and 14 female Fischer 344 rats and B6C3F1 mice to 0, 50, 250 or 1000 ppm (0, 205, 1024 or 4097 mg/m^3) 6 hours/day, 5 days/week for 14 weeks. The parameters examined were clinical observation, body weight, organ weights (heart, kidney, liver, lungs and testes), urinalysis (rats only), serum chemistry (rats only) and hematologic, ophthalmologic, gross pathologic and histologic evaluations.

The results of the study showed significantly increased absolute and relative liver weights in male mice and rats exposed at 1000 ppm MIBK. Male mice exposed at 250 ppm MIBK had an increase in absolute liver weight ($p<0.05$). No effects on liver weights were noted in female mice or rats. An increase in the incidence of hyaline droplets in the proximal tubules in male rats exposed at 250 and 1000 ppm was also noted. This effect was not observed in female rats or male and female mice. No other chemical-related changes were noted in either MIBK-exposed rats or mice.

Spencer et al. (1975) exposed a group of six rats to 1500 ppm (6140 mg/m³) MIBK, 6 hours/day, 5 days/week, for up to 5 months and compared them with a control group of three rats. No effects on body weight gain or neurological function occurred. Histopathological examination, limited to selected peripheral nerves, revealed invaginations of the Schwann cells, focal swelling and dilated mitochondrial remnants in the adaxonal segments of the tibial and ulnar nerves. The authors attributed these findings to contamination of the MIBK with methyl n-butyl ketone, which caused similar effects in a companion study.

Geller et al. (1979) conducted behavioral experiments with four juvenile male baboons exposed to 50 ppm (205 mg/m³) MIBK 24 hours/day for 7 days. The baboons were exposed to other ketones as well, but at least 1 month elapsed between the exposures to different chemicals. Effects were evaluated using a delayed match-to-sample discrimination task. Accuracy of performance was minimally affected, but response time was slowed by MIBK.

Abou-Donia et al. (1985) conducted inhalation experiments with groups of five hens exposed to 1000 (4090 mg/m³) MIBK for 90 days followed by a 30-day observation period. MIBK exposure resulted in leg weakness with subsequent recovery.

3.2. CHRONIC

3.2.1. Oral. Chronic oral toxicity studies with MIBK could not be located in the available literature.

3.2.2. Inhalation. There are several reports of humans occupationally exposed to MIBK vapors. Linari et al. (1964) reported that 19 workers near a centrifuge were exposed to 500 ppm (2050 mg/m³) MIBK for 20-30 minutes/day, while concentrations elsewhere in the room were 80 ppm (330 mg/m³).

Over 50% of the workers experienced nausea, headache, burning in the eyes and weakness; some also experienced somnolence, insomnia and intestinal pain, and four appeared to have slightly enlarged livers. Armeli et al. (1968) conducted a similar study of this workplace 5 years later, when hygiene improvements resulted in MIBK concentrations of 100-105 ppm (410-430 mg/m³) near the centrifuge during its 15-30 minutes of operation and 50 ppm (205 mg/m³) elsewhere in the room. A few workers still experienced gastrointestinal and CNS symptoms, and slight liver enlargement was found in two workers. Elkins (1959) reported that workers exposed to MIBK levels of 100 ppm (410 mg/m³) complained of headache, nausea and respiratory irritation.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Data concerning teratogenicity or other reproductive effects of MIBK could not be located in the available literature.

3.3.2. Inhalation. Union Carbide Corporation (1984) conducted teratogenicity studies using rats and mice following inhalation exposure to MIBK. Groups of 25 pregnant Fischer 344 rats and 25 CD-1 mice were exposed to 0, 300, 1000 or 3000 ppm (0, 1229, 4097 or 12,290 mg/m³) MIBK vapors, 6 hours/day on gestation days 6 through 15. Rats were sacrificed on day 21 and mice on day 18 of gestation.

Maternal toxicity was observed in rats and mice. Rats exhibited reduction in body weight, loss of coordination, negative tail and toe pinch, partial paralysis, muscular weakness in hindlimbs, piloerection, lacrimation and red perioral encrustation. At sacrifice, relative kidney weights of the dams were also significantly increased compared with controls. In mice, no changes in body weight were noted; however, 3/25 mice died. Clinical signs of toxicity included irregular gait, partial paralysis, hypoactivity,

ataxia, negative toe pinch, unkempt fur and lacrimation. At sacrifice, absolute and relative liver weights were significantly increased.

Results of reproductive parameters showed no treatment-related effects on the number of corpora lutea, total implantations per litter, percent preimplantational loss, percent live fetuses or sex ratio in either rats or mice. Fetal weight per litter was significantly reduced in rats at 300 and 3000 ppm but not at the 1000 ppm exposure level. In mice, there was a significant decrease in the number of live births and fetal body weights per litter at 3000 ppm. Teratogenic examination revealed no statistically significant increases in malformations in either rats or mice. An increased incidence of poorly ossified or unossified skeletal elements was observed in rats and mice at 3000 ppm. Investigators concluded that inhalation exposure of pregnant rats and mice to MIBK at $\geq$3000 ppm was associated with maternal and fetal toxicity but not teratogenicity.

3.4. TOXICANT INTERACTIONS

Plaa and Ayotte (1985) studied potentiation of TLC toxicity in rats by MIBK pretreatment. Pretreatment of male Sprague-Dawley rats with 3.75 or 7.5 mmol/kg for 3 or 7 days enhanced the cholestasis caused by intravenous injections of TLC. Another study found MIBK to potentiate the hepatonecrogenic properties of chloroform and carbon tetrachloride (Vezina et al., 1985).

The inhalation studies by Abou-Donia et al. (1985) and Geller et al. (1979), also contained information about the interaction of MIBK with other toxicants. In the Geller et al. (1979) baboon behavioral study, administration of MIBK and methyl ethyl ketone together caused an increase in responses and a decrease in response times, effects not seen when the chemicals were administered individually. Abou-Donia et al. (1985) exposed

hens to mixtures of MIBK and n-hexane (1000 ppm) to study the effect of MIBK on n-hexane-induced neurotoxicity. They found that exposure to the mixture potentiated clinical signs of n-hexane-induced neurotoxicity, which were MIBK-dose-related in intensity. The ability of MIBK to potentiate n-hexane neurotoxicity may have been due to its ability to induce liver microsomal enzymes resulting in increased activation of n-hexane to more toxic metabolites (Abou-Donia et al., 1985).

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenic potential of MIBK by oral or inhalation exposure to humans could not be located in the available literature.

4.2. BIOASSAYS

Studies regarding the carcinogenicity of MIBK to animals exposed by the oral or inhalation routes could not be located in the available literature.

4.3. OTHER RELEVANT DATA

In a report by the Chemical Manufacturers Association (1984), MIBK was found to be negative for reverse mutation in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 both with and without S-9 metabolic activation. MIBK was also found to be negative for unscheduled DNA synthesis and in the mouse micronucleus assay. The mouse lymphoma assay for forward gene mutation was positive, however, only at a concentration that produced 97% cell death. MIBK was also studied in a cell transformation assay in the presence and absence of S-9 metabolic activation. This assay showed positive results in the nonactivated but not in the activated cultures; however, a repeat assay indicated that MIBK did not significantly increase the number of transformed foci in either the presence or absence of S-9.

4.4. WEIGHT OF EVIDENCE

Data concerning potential carcinogenicity of MIBK could not be located in the available literature. MIBK has not been classified; however, according to the U.S. EPA (1986b) Guidelines for Carcinogen Risk Assessment, MIBK would most appropriately be classified as a Group D chemical, i.e., not classifiable as to human carcinogenicity.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1986) recommended a TLV-TWA of 50 ppm (205 mg/m³) and a TLV-STEL of 75 ppm (300 mg/m³) for occupational atmospheric exposure to MIBK. This value was based on the animal data of MacEwen et al. (1971) and the human data of Elkins (1959), which indicated that adverse effects (headache and nausea in humans and increased kidney weight in animals) occurred at 100 ppm (410 mg/m³). NIOSH (1978) also proposed a TWA limit of 50 ppm (205 mg/m³). The OSHA (1983) standard for MIBK is 100 ppm (410 mg/m³).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). The study by Microbiological Associates (1986) provides the only suitable basis for deriving an RfD_{SO}. In this study, MIBK was administered to groups of 30 male and 30 female Sprague-Dawley rats by gavage in corn oil daily for 13 weeks. Nephrotoxicity and increased liver and kidney weights occurred in males and females at 1000 mg/kg/day and to a lesser extent at 250 mg/kg/day. No adverse effects occurred at 50 mg/kg/ day. By dividing this NOEL by an uncertainty factor of 100, to account for interspecies extrapolation and intraspecies variations in sensitivity, an RfD_{SO} value of 0.5 mg/kg/day (35 mg/day) can be derived.

6.1.2. Inhalation (RfD_{SI}). Subchronic inhalation studies available for consideration in the derivation of an RfD_{SI} are limited to the 90-day continuous exposure study by MacEwen et al. (1971) in which rats were exposed to 100 ppm (410 mg/m³) MIBK and a 14-week intermittent exposure study by Union Carbide Corp. (1983b) in which rats and mice were exposed to 0, 50, 250 and 1000 ppm (0, 205, 1024 and 4097 mg/m³) MIBK. Because the MacEwen et al. (1971) study was conducted under reduced atmospheric and increased oxygen concentration and because only one exposure level was tested which did not define a NOAEL, the Union Carbide Corp. (1983b) study was considered more appropriate for estimation of an RfD_{SI}. Exposure to 250 ppm (1024 mg/m³) MIBK for 6 hours/day, 5 days/week resulted in an increase in absolute liver weights in male mice and an increase in hyaline droplets of the proximal tubules of the kidney in male rats. No effect was seen in either male or female rats or mice at 50 ppm (205 mg/m³). Therefore, the 50 ppm dose was considered a NOEL and the 250 ppm dose a LOAEL. An equivalent inhalation dose for rats was calculated by multiplying the NOEL exposure dose (205 20/m³) by the animal breathing rate (0.223),

dividing by the reference body weight for rats (0.35 kg) and multiplying by the factors of 6 hours/24 hours and 5 days/7days to expand to continuous exposure. The resultant inhalation dose is 23.3 mg/kg/day. An RfD_{SI} of 0.23 mg/kg/day or 16 mg/day for a 70 kg man was derived by applying an uncertainty factor of 100, 10 to account for interspecies variation and 10 to provide greater protection for unusually sensitive individuals.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). Data regarding the chronic oral toxicity of MIBK could not be located in the available literature. The 13-week rat study by Microbiological Associates (1986) provides suitable oral subchronic data for deriving an RfD_0. The resulting RfD_0 is 0.05 mg/kg/day (3.5 mg/day), which is the same as the RfD value calculated by U.S. EPA (1986a).

The data from the 13-week rat gavage study by Microbiological Associates (1986) are the only bases suitable for deriving CSs for oral exposure. These calculations are summarized in Table 6-1. Using standard methodology and dividing by an uncertainty factor of 10 to account for use of subchronic data, a human MED of 261 mg/day and an RV_d of 1.9 were calculated. An RV_e of 4 was assigned to the effect, resulting in a CS (RV_d x RV_e) of 7.6.

6.2.2. Inhalation (RfD_I). Data concerning the chronic inhalation toxicity of MIBK could not be located in the available literature. An RfD_I for MIBK can be derived by the application of an additional uncertainty factor of 10 to the RfD_{SI} of 16 mg/day derived from the subchronic study by Union Carbide Corporation (1983b). The resultant RfD_I of 1.6 mg/day for 70 kg adult is recommended for inhalation exposure to MIBK.

TABLE 6-1

Composite Scores for Toxicity of MIBK[a]

Species/Sex	Route	Exposure/Dosage	Human MED (mg/day)	RV_d	Effect	RV_r	CS	Reference
Rat/female	oral	1000 mg/kg/day for 90 days[a]	1036.1[b,c]	1	General nephropathy, increased relative kidney and liver weight	7	7	Microbiological Associates, 1986
Rat/female	oral	250 mg/kg/day for 90 days[a]	261[b,d]	1.9	Increased relative kidney weight	4	7.6	Microbiological Associates, 1986
Human	inhalation	100 ppm (410 mg/m³) occupational[e]	2930	1	Headache, nausea, respiratory irritation	4	4	Elkins, 1959
Rat/male	inhalation	410 mg/m³ continuous 90 days (261 mg/kg/day)[e,f]	312[b]	1.8	Histopathological effects including necrosis in kidney	6	10.8	MacEwen et al., 1971
Rat	inhalation	1500 ppm (6140 mg/m³) 6 hours/day, 5 days/week, 5 months (699 mg/kg/day)[e,g]	837[b]	1.1	Degenerative changes in brain cells	6	6.6	Spencer et al., 1975
Rat/male	inhalation	250 ppm (1024 mg/m³) 6 hours/day, 5 days/week, 14 weeks (116.5 mg/kg/day)[e,g]	139	2.3	Hyaline droplets proximal tubules of kidney	5	11.5	Union Carbide Corp., 1983b

[a]Administered daily by gavage in corn oil for 13 weeks.

[b]Divided by an uncertainty factor of 10 to account for extrapolation from subchronic data.

[c]Reference rat inhalation rate = 0.223 m³/day (U.S. EPA, 1980b)

[d]Data presented only for females, which had some critical effects in males but whose lesser body weights result in lower human MEDs and higher Rv_ds. Body weights of 0.233 and 0.227 kg at 250 and 1000 mg/kg/day are midpoint values taken from tabular data provided by investigators.

[e]Reference humans inhalation rate = 10m³/workday (U.S. EPA 1980b)

[f]Reference rat body weight assumed 0.35 kg (U.S. EPA, 1980a)

ACGIH (1986) cited an occupational exposure study reported by Elkins (1959) in which workers involved in the waterproofing of boots were exposed to 100 ppm (410 mg/m³) MIBK and complained of headache and nausea. An RfD_I for MIBK could be derived using the TLV of 50 ppm based on the above study by Elkins (1959) and animal studies by Geller et al. (1979). However, because of the uncertainty associated with the estimation of concentrations in the human studies, an RfD_I derived from the RfD_{SI} is more appropriate (Union Carbide Corp., 1983b).

CSs can be calculated for the effects of MIBK by inhalation exposure. Several reports (Linari et al., 1964; Armeli et al., 1968; Elkins, 1959) associate exposure in the workplace to irritation, nausea, headache, disturbed sleep and CNS symptoms. Elkins (1959) appears to be the only study to quantify the effects of MIBK in humans; the author reported headache, nausea and respiratory irritation in workers exposed to 100 ppm. In the 90-day continuous inhalation rat study at 410 mg/m³ (MacEwen et al., 1971) and the 14-week rat study at 1024 mg/m³ (Union Carbide Corp., 1983b), histopathological changes were observed in the kidneys; in the 5-month rat study by Spencer et al. (1975), 1500 ppm (6140 mg/m³) was associated with histopathological changes in the brain. Inhalation concentrations in mg/m³ were expanded to continuous exposure, multiplied by reference inhalation rates and divided by appropriate measured or assumed animal body weights (if appropriate) to estimate exposed dose in terms of mg/kg/day. From animal studies, human MEDs were calculated (see Section 6.2.1.). These CSs are presented in Table 6-1. The highest CS (11.5) based on histopathological effects in the kidneys of rats exposed by inhalation (Union Carbide Corp., 1983b), is appropriately chosen to represent the toxicity of MIBK.

6.3. CARCINOGENIC POTENCY (q_1*)

Data concerning possible carcinogenicity of MIBK could not be located in the available literature.

7. REFERENCES

Abou-Donia, M.B., D.M. Lapadula, G. Campbell and P.R. Timmons. 1985. The synergism of n-hexane-induced neurotoxicity by methyl isobutyl ketone following subchronic (90 days) inhalation in hens: Induction of hepatic microsomal cytochrome P-450. Toxicol. Appl. Pharmacol. 81(10): 1-16.

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH. p. 402.

Armeli, G., F. Linari and G. Martovano. 1968. Rellevi Clinici ed Ematochimici in operai Esposti all'azione di un Chetone Superione (MIBK) Ripetui a distanza di S anni. Lav. Um. 20: 418. (Ital.) (Cited in ACGIH, 1986)

Chemical Manufacturers Association. 1984. Voluntary testing program under Section 4. Toxic Substances Control Act. Submission of test data Vol. 1: MIBK Mutagenicity and Teratology Studies. U.S. EPA/OPTS Public Files OTS 0000355-0.

Cox, R.A., R.G. Derwent and M.R. Williams 1980. Atmospheric photooxidation reactions rates, reactivity and mechanism for reaction of organic compound with hydroxyl radicals. Environ. Sci. Technol. 14: 57-61.

Darnall, K.R., A.C. Lloyd, A.M. Winder and J.N. Pitts, Jr. 1976. Reactivity scales for atmospheric hydrocarbons based on reaction with hydroxyl radicals. Environ. Sci. Technol. 10: 692-696.

DiVincenzo, G.D. and W.J. Krasavage. 1974. Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. Am. J. Ind. Hyg. Assoc. 35: 21-29.

Elkins, H.B. 1959. The Chemistry of Industrial Toxicology, 2nd ed. p. 121. John Wiley and Sons, NY. (Cited in ACGIH, 1986)

Francis, A.J., C.R. Iden, B.J. Nine and C.K. Chang. 1980. Characterization of organics in leachates from low-level radioactive waste disposal sites. Nuclear Technol. 50: 158-163.

Geller, I., E. Gause, H. Kaplan and R.J. Hartmann. 1979. Effects of acetone, methyl ethyl ketone and methyl isobutyl ketone on a match-to-sample task in the baboon. Pharmacol. Biochem. Behav. 11(4): 401-406.

Hansch, C., J.E. Quinlan and G.L. Lawrence. 1968. The linear free-energy relationship between partition coefficients and the aqueous solubility of organic liquids. J. Org. Chem. 33(1): 347.

IARC (International Agency for Research on Cancer). 1979. Chemicals and Industrial Processor Associated with Cancer in Humans. IARC monographs, Supplement 1. WHO, Lyon, France. 19: 13.

Lande, S.S., P.R. Durkin, D.H. Christopher, P.H. Howard and J. Saxena. 1976. Investigation of selected potential environmental contaminants: Ketones solvents. U.S. NTIS Public Report #252970.

Linari, F., G.C. Coscia, G. Martovano and G. Perrelli. 1964. Aminoaciduria in occupational intoxication. Arch. Sci. Med. 116(6): 336-347. (Cited in ACGIH, 1986)

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. McGraw Hill Book Co., New York. p. 4-9, 5-5.

MacEwen, J.D., E.H. Vernot and C.C. Haun. 1971. Effect of 90-day continous exposure to methylisobutylketone on dogs, monkeys and rats. NTIS AD-730291. 29 p.

Microbiological Associates. 1986. Subchronic toxicity of methyl isobutyl ketone in Sprague-Dawley rats. Preliminary report for Research Triangle Institute, RTP, NC. Study No. 5221. 04. January.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a recommended standard occupational exposure to ketone. DHEW Publ. No. (NIOSH) 78-173.

OSHA (Occupational Safety and Health Administration). 1983. OSHA Safety and Health Standards. 29: CFR 1910.1000.

Plaa, G.L. and P. Ayotte. 1985. Taurolithocholate-induced intrahepatic cholestasis: Potentiation by methyl isobutyl ketone and methyl n-butyl ketone in rats. Toxicol. Appl. Pharmacol. 80(2): 228-234.

Rathbun, R.E. and D.Y. Tai. 1982. Volatilization of ketones. Water Air Soil Pollut. 17: 281-293.

Sadtler. n.d. Sadtler Standard UV Spectra No. 21. Sadtler Research Laboratory, Philadelphia, PA.

Sawhney, B.L. and R.P. Kozloski. 1984. Organic pollutants in leachates from landfill sites. J. Environ. Qual. 13: 349-352.

Silverman, L., et al. 1946. Further studies on sensory response to certain industrial solvent vapors. J. Ind. Hyg. Tox. 28: 262. (Cited in ACGIH, 1986)

Spencer, P.S., H.H. Schaumburg, R.L. Raleigh and C.J. Terhaar. 1975. Nervous system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch. Neurol. 32: 219-222.

Swann, R.L., D.A. Laskowski, P.J. McCall, K. VanderKuy and H.J. Dishburger. 1984. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Res. Rev. 85: 17-28.

Union Carbide Corporation. 1983a. Comparative toxicity to rats of methoxyacetone and five other aliphatic ketones in their drinking water. U.S. EPA public files OTS 0750206068.

Union Carbide Corporation. 1983b. Ninety-day inhalation study in rats and mice sponsored by CMA. U.S. EPA/OTS public files 0750507469.

Union Carbide Corporation. 1984. A teratologic evaluation of methyl isobutyl ketone in Fischer 344 rats and CD-1 mice following inhalation exposure. U.S. EPA/OTS public files 0750507469.

U.S. EPA. 1980a. Hazard Profile for Methyl Isobutyl Ketone. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effect Assessment Chapters of the Consent Decree Water Quality Criteria Documents. Federal Register. 45(231): 49347-49357.

U.S. EPA. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assesment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986a. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Methyl Isobutyl Ketone. Online (verification date 5/30/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986b. Guidelines for carcinogen risk assessment, request for comments. Federal Register. 51(185): 33992-34003.

Vezina, M., P. Ayotte and G.L. Plaa. 1985. Potentiation of necrogenic and cholestatic liver injury by 4-methyl-2-pentanone. Canadian Fed. Biol. Soc. 28: 221. (Cited in Plaa and Ayotte, 1985)

01800h

APPENDIX

Summary Table for MIBK

	Species	Experimental/Dose	Effect	Reference Dose (RfD) (mg/day)	Reference
Inhalation					
RfD_{SI} (formerly AIS)	rat	50 ppm (205 mg/m³) (0.23 mg/kg/day)	NOEL; higher doses associated with hyaline droplet degeneration in kidney.	16	Union Carbide Corp., 1983b
RfD_I (formerly AIC)	rat	50 ppm (205 mg/m³) (0.23 mg/kg/day)	NOEL	1.6	Union Carbide Corp., 1983b
Oral					
RfD_{SO}	rat	50 mg/kg/day by gavage in corn oil for 13 weeks	NOAEL for increased liver and kidney weights	35.0	Microbiological Associates, 1986
RfD_{SO}	rat	50 mg/kg/day by gavage in corn oil for 13 weeks	NOAEL for increased liver and kidney weights	3.5	Microbiological Associates, 1986
CS	rat	250 ppm (1024 mg/m³) 6 hours/day, 5 days/week for 14 weeks (116.5 mg/kg/day)	Hyaline droplet formation in the proximal tubules of kidney $2V_e$ = 5.	CS = 11.5	Union Carbide Corp., 1983b

06/09/87